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# Low-Flow, Low-Gradient Severe Aortic Stenosis Despite Normal Ejection Fraction Is Associated With Severe Left Ventricular Dysfunction as Assessed by Speckle-Tracking Echocardiography

## A Multicenter Study

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**Background**—Low-flow low-gradient (LFLG) is sometimes observed in severe aortic stenosis (AS) despite normal ejection fraction, but its frequency and mechanisms are still debated. We aimed to describe the characteristics of patients with LFLG AS and assess the presence of longitudinal left ventricular dysfunction in these patients.

**Methods and Results**—In a multicenter prospective study, 340 consecutive patients with severe AS and normal ejection fraction were studied. Longitudinal left ventricular function was assessed by 2D-strain and global afterload by valvulo-arterial impedance. Patients were classified according to flow and gradient: low flow was defined as a stroke volume index  $\leq 35$  mL/m<sup>2</sup>, low gradient as a mean gradient  $\leq 40$  mm Hg. Most patients (n=258, 75.9%) presented with high-gradient AS, and 82 patients (24.1%) with low-gradient AS. Among the latter, 52 (15.3%) presented with normal flow and low gradient and 30 (8.8%) with LFLG. As compared with normal flow and low gradient, patients with LFLG had more severe AS (aortic valve area =  $0.7 \pm 0.12$  cm<sup>2</sup> versus  $0.86 \pm 0.14$  cm<sup>2</sup>), higher valvulo-arterial impedance ( $5.5 \pm 1.1$  versus  $4 \pm 0.8$  mm Hg/mL/m<sup>2</sup>), and worse longitudinal left ventricular function (basal longitudinal strain =  $-11.6 \pm 3.4$  versus  $-14.8 \pm 3\%$ ;  $P < 0.001$  for all).

**Conclusions**—LFLG AS is observed in 9% of patients with severe AS and normal ejection fraction and is associated with high global afterload and reduced longitudinal systolic function. Patients with normal-flow low-gradient AS are more frequent and present with less severe AS, normal afterload, and less severe longitudinal dysfunction. Severe left ventricular longitudinal dysfunction is a new explanation to the concept of LFLG AS. (*Circ Cardiovasc Imaging*. 2012;5:27-35.)

**Key Words:** aorta ■ stenosis ■ echocardiography ■ valves

Assessment of aortic stenosis (AS) severity is still challenging. Severe AS usually is defined as mean gradient  $> 40$  mm Hg, aortic valve area (AVA)  $< 1$  cm<sup>2</sup>, or indexed AVA  $< 0.6$  cm<sup>2</sup>/m<sup>2</sup>.<sup>1,2</sup> However, discrepancies are frequently observed between the mean gradient and the valve area in a single patient.<sup>3-5</sup> These discrepancies are easy to understand in patients with low cardiac output secondary to reduced left ventricular ejection fraction (LVEF), but also may occur in patients with apparently normal left ventricular (LV) function.<sup>6</sup>

### Editorial see p 6 Clinical Perspective on p 35

These paradoxical low-gradient severe AS, despite preserved LVEF, were first described by Hachicha et al,<sup>7</sup> who found up to 35% of such cases among patients with AS and normal LV function. These patients were characterized by a low flow, defined by a stroke volume index (SVi)  $\leq 35$  mL/m<sup>2</sup>, and had higher valvulo-arterial impedance ( $Z_{va}$ ) and smaller left ventricular dimensions.

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Although these patients have been reported to carry a bad prognosis,<sup>7,8</sup> several uncertainties persist concerning this group of patients, about its frequency, pathophysiology, and prognosis.<sup>3,4</sup>

First, many patients present with a low flow, but high (>40 mm Hg) mean gradient. Conversely, and more importantly, some patients may present with a mean gradient ≤40 mm Hg in spite of a normal flow,<sup>3–5</sup> and thus don't fulfill criteria for low-flow low-gradient (LFLG) AS. Whether these patients truly have severe AS is still debated.<sup>3,4</sup>

Second, the explanation for this low flow despite normal LVEF is not completely elucidated. Although elevated global afterload, as attested by a high valvulo-arterial impedance, seems to be the main mechanism, subtle LV dysfunction also has been suspected in these patients, even though their LVEF is normal.<sup>6</sup> It was first evidenced by a low midwall fractional shortening<sup>7,9</sup> and stroke work index. More recently, 2D strain has been shown to be useful for the early detection of longitudinal LV dysfunction in patients with AS.<sup>10–12</sup> However, no large study has assessed prospectively the value of 2D strain in assessing early LV dysfunction in this particular group, and it is not known whether LV longitudinal dysfunction is more severe in patients with LFLG AS as compared with other patients with AS.

For these reasons, we conducted a prospective multicenter study aiming to:

describe the characteristics of patients with a normal LVEF and severe AS, with low flow or low gradient.  
assess the presence of longitudinal LV dysfunction in these patients using 2D strain imaging.

## Methods

### Patient Sample

During a 2-year period ending June 2010, patients from 5 centers (Marseille, Liège, Rennes, Bordeaux, and Montpellier) with severe aortic stenosis (aortic valve area <0.6 cm<sup>2</sup>/m<sup>2</sup>) and normal LVEF (≥50%) were prospectively included in our study. Exclusion criteria were more than mild other valvulopathy, LVEF <50%, segmental hypokinesia/akinesia, and acute coronary syndrome <3 months. This study was approved by Institutional Review Committee and was conducted according to the principles outlined in the Declaration of Helsinki.

### Clinical Data

Clinical data included New York Heart Association class, age, gender, history of smoking, treated hypertension or hypercholesterolemia, diabetes, obesity, and coronary disease. Systemic arterial pressure was measured with the use of an arm-cuff sphygmomanometer at the time of the echocardiographic study. Mean arterial pressure (MAP) was estimated with the formula MAP=2/3 diastolic arterial pressure (DAP) +1/3 systolic arterial pressure (SAP).

### Doppler Echographic Data

Conventional 2D echocardiography was performed using commercially available equipment (Vivid-7, General Electric Medical Systems, Horten, Norway). Data were acquired with a M3S 3.5 MHz transducer. M-mode, 2-dimensional, color Doppler and pulsed-wave and continuous-wave Doppler data were stored on a dedicated workstation for offline analysis (EchoPAC, GE Healthcare, Horten, Norway). A complete echocardiographic and Doppler examination was performed in all patients, as recommended by Hachicha et al.<sup>7</sup>

The following parameters were systematically measured.

### Aortic Stenosis Severity

The aortic valve area was calculated using the continuity equation, and indexed to the body surface area (BSA). Mean transvalvular gradient (MG) was obtained using the modified Bernoulli equation. The energy loss index (ELI) was calculated with the following formula (aortic cross-sectional area [Aa])<sup>13</sup>:

$$ELI = \frac{(AVA \times Aa) / (Aa - AVA)}{BSA}$$

### LV Afterload

Valvulo-arterial impedance was measured using the formula:

$$Z_{va} = \frac{SAP + MG}{SV_i}$$

Systemic vascular resistance was calculated using the formula (cardiac output [CO]):

$$SVR = \frac{80 \times MAP}{CO}$$

Systemic arterial compliance was estimated using the following formula:

$$SAC = \frac{SV_i}{(SAP - DAP)}$$

### LV Geometry

Left ventricular dimensions were measured using M-Mode parasternal long-axis view. LV mass was estimated using the American Society of Echocardiography/European Association of Echocardiography recommendations.<sup>14</sup>

### LV Systolic Function

The LVEF was assessed in all patients using the biplane Simpson method. Stroke volume was calculated by multiplying the left ventricular outflow tract area by the left ventricular outflow tract velocity integral measured by PW-Doppler and was indexed for body surface area, to give SV<sub>i</sub>.

Midwall fractional shortening (MWFS) was calculated using the formula (left ventricular internal diameter [LVID], posterior wall thickness [PWT]):<sup>15</sup>

$$MWFS = \frac{(LVIDd/2 + PWTd/2) - (LVIDs/2 + PWTs/2)}{(LVIDd/2 + PWTd/2)}$$

Stroke work was calculated with the following formula, and then indexed to the LV mass:

$$SW = (MAP + MG) \times SV \times 0.0136$$

### Two-Dimensional Strain Study

Strain quantification was performed offline by using commercially available software (EchoPAC, GE Healthcare, Horten, Norway). We recorded the parasternal midventricular short-axis plane to calculate radial and circumferential strain, and the apical 4-, 2-, and 3-chambers views to calculate global longitudinal strain (GLS).

A line was traced along the inner border of the endocardium on an end-systolic frame. A region of interest was then automatically defined between the endocardial and epicardial borders. Two-dimensional gray-scale images were acquired in the standard apical 4-chamber, 3-chamber, and 2-chamber views at a frame rate >80 frames/s.

GLS was automatically calculated from the 3 apical views strain. A radial and circumferential strain score was determined as the average of the peak systolic strains of 6 myocardial segments.

To ensure the standardization of strain analysis across sites, several precautions were taken, including the use of the same dedicated workstation for offline analysis in the 5 centers, the systematic use and filling of the same data sheet, including an accompanying explanatory sheet, and the review of standardized images in the different centers. In addition, an additional strain variability study was performed (see below).

**Table 1. Characterization of 340 Patients Based on Flow ( $\leq$  or  $>35$  mL/m<sup>2</sup>) and Gradient ( $\leq$  or  $>40$  mm Hg)**

AVA $\leq 0.6$ cm <sup>2</sup> /m <sup>2</sup>	Normal Flow SVi $>35$ mL/m <sup>2</sup>	Low Flow SVi $\leq 35$ mL/m <sup>2</sup>	
High gradient MG $>40$ mm Hg	Group 1	Group 2	
	Normal flow, high gradient	Low flow, high gradient	
	n=213 (62.7%)	n=45 (13.2%)	
	LVEF: 66.8 $\pm$ 8 %	LVEF: 63.7 $\pm$ 8.2 %	
	MG: 57 $\pm$ 13.5 mm Hg	MG: 64.4 $\pm$ 16.3 mm Hg	n=258
	AVA: 0.79 $\pm$ 0.17 cm <sup>2</sup>	AVA: 0.46 $\pm$ 0.11 cm <sup>2</sup>	(75.9%)
	AVAi: 0.44 $\pm$ 0.08 cm <sup>2</sup> /m <sup>2</sup>	AVAi: 0.26 $\pm$ 0.05 cm <sup>2</sup> /m <sup>2</sup>	
	Z <sub>va</sub> : 4.1 $\pm$ 0.8 mm Hg/mL/m <sup>2</sup>	Z <sub>va</sub> : 6.7 $\pm$ 1.3 mm Hg/mL/m <sup>2</sup>	
	GLS: -16.5 $\pm$ 3.4 %	GLS: -14.1 $\pm$ 3.5 %	
Low gradient MG $\leq 40$ mm Hg	Group 3	Group 4	
	Normal flow, low gradient	Low flow, low gradient	
	n=52 (15.3%)	n=30 (8.8%)	
	LVEF: 64.6 $\pm$ 7.3 %	LVEF: 63 $\pm$ 9.3 %	
	MG: 34.4 $\pm$ 4.6 mm Hg	MG: 32.7 $\pm$ 5.7 mm Hg	n=82
	AVA: 0.86 $\pm$ 0.14 cm <sup>2</sup>	AVA: 0.7 $\pm$ 0.12 cm <sup>2</sup>	(24.1%)
	AVAi: 0.49 $\pm$ 0.07 cm <sup>2</sup> /m <sup>2</sup>	AVAi: 0.38 $\pm$ 0.08 cm <sup>2</sup> /m <sup>2</sup>	
	Z <sub>va</sub> : 4 $\pm$ 0.8 mm Hg/mL/m <sup>2</sup>	Z <sub>va</sub> : 5.5 $\pm$ 1.1 mm Hg/mL/m <sup>2</sup>	
	GLS: -16.5 $\pm$ 3.5 %	GLS: -15.5 $\pm$ 4.1 %	
	n=265 (78%)	n=75 (22%)	n=340
			(100%)

AVA indicates aortic valve area; AVAi, aortic valve area index; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; MG, mean gradient; SVi, stroke volume index; Z<sub>va</sub>, valvulo-arterial impedance.

## Groups Definition

Patients were separated into 4 groups, according to their SVi ( $>$  or  $\leq 35$  mL/m<sup>2</sup>), and their MG ( $>$  or  $\leq 40$  mm Hg), as proposed by Hachicha et al<sup>7</sup> and Dumesnil et al.<sup>5</sup>

Group 1: normal flow high gradient: SVi  $>35$  mL/m<sup>2</sup> and MG  $>40$  mm Hg

Group 2: low flow, high gradient: SVi  $\leq 35$  mL/m<sup>2</sup> and MG  $>40$  mm Hg

Group 3: normal flow, low gradient (NFLG): SVi  $>35$  mL/m<sup>2</sup> and MG  $\leq 40$  mm Hg

Group 4: low flow, low gradient: SVi  $\leq 35$  mL/m<sup>2</sup> and MG  $\leq 40$  mm Hg.

In addition, since women have been reported to have higher LV mass in response to aortic stenosis and to have more frequently a low-flow than a normal-flow aortic stenosis,<sup>7</sup> a specific analysis of differences between men and women was performed, both in the overall population and in each group.

## Statistical Analysis

All continuous results are expressed as mean  $\pm$  standard deviation or as percentages. We used the binomial approach to estimate 95% confidence intervals (CI) of the percentages. Comparisons of the categorical variables among the 4 groups were performed by using the Fisher exact test. Comparisons of the continuous variables among the 4 groups were performed by using the non-parametric Kruskal-Wallis test. Then, when a statistically significant difference was detected in Kruskal-Wallis test, Mann-Whitney U test and Bonferroni correction were used in each pair for post hoc analysis. Linear regression was used to assess the LV dysfunction, appraised by the measure of basal longitudinal strain, according to the group (with patients NFLG as reference). Confounders systematically considered for the analysis corresponded to classical demographical factors (age, sex) and to factors identified in univariate analysis (AVA, Z<sub>va</sub>). We also used likelihood ratio test for testing interactions.

Furthermore, to assess the variability of the measures using 2D-strain, 13 randomly selected patients were evaluated twice by the same observer (JA) for intra-observer variability, by 2 different observers in the same center (JA and GH) for inter-observer variability, and by a third observer from another center (ED) for interinstitutional variability. Variability was quantified computing intraclass correlation coefficient (ICC), with 95% CI obtained using bootstrap method with 1000 replicates.

All statistical analyses were performed with R, using the package psy and the version 2.12, and probability values  $<0.05$  were considered statistically significant with the use of 2-tailed tests.

## Results

During the study period, 340 patients were diagnosed as having severe aortic stenosis (aortic valve area  $<0.6$  cm<sup>2</sup>/m<sup>2</sup>) and normal LVEF ( $\geq 50\%$ ). The repartition of the 340 patients among the 4 groups is presented in Table 1. Table 2 represents the repartition of patients among the 4 groups according to the center. Table 3 compares the clinical and echocardiographic characteristics among the 4 groups. Table 4 represents their strain values.

**Table 2. Repartition of Patients Among the 5 Centers**

	Group 1	Group 2	Group 3	Group 4	TOTAL
Marseille	109 (71.7%)	19 (12.5%)	13 (8.6%)	11 (7.2%)	152
Montpellier	19 (54.3%)	5 (14.3%)	7 (20%)	4 (11.4%)	35
Rennes	39 (78%)	2 (4%)	7 (14%)	2 (4%)	50
Bordeaux	24 (51.1%)	12 (25.5%)	7 (14.9%)	4 (8.5%)	47
Liège	22 (39.3%)	7 (12.5%)	18 (32.1%)	9 (16.1%)	56
Global	213 (62.7%)	45 (13.2%)	52 (15.3%)	30 (8.8%)	340

**Table 3. Comparison of Clinical and Echocardiographic Characteristics Among the 4 Groups**

	Group 1 SVi>35 MG>40 n=213	Group 2 SVi≤35 MG>40 n=45	Group 3 SVi>35 MG≤40 n=52	Group 4 SVi≤35 MG≤40 n=30
<b>Clinical characteristics</b>				
Age (y)	71.3±11.7 ns	75.2±9.2	73.8±10	74.6±14.7
Men (%)	69 0.008	44	54	63
BSA (m <sup>2</sup> )	1.8±0.18 ns	1.81±0.21	1.77±0.18	1.85±0.17
Hypertension (%)	67 0.04	71	78	56
Diabetes (%)	20 0.03	30	36	41
SAP (mm Hg)	139±22 ns	133±21	143±23	133±21
DAP (mm Hg)	74±13 ns	72±13	74±11	70±12
<b>Aortic stenosis severity</b>				
AVA (cm <sup>2</sup> )	0.79±0.17 cm <sup>2</sup> †††,††,\$	0.46±0.11 cm <sup>2</sup> ***,†††,\$\$\$	0.86±0.14 cm <sup>2</sup> **,†††,\$\$\$	0.70±0.12 cm <sup>2</sup> *,†††,†††
AVAI (cm <sup>2</sup> /m <sup>2</sup> )	0.44±0.08†††,†††,\$\$	0.26±0.05***,†††,\$\$\$	0.49±0.07***,†††,\$\$\$	0.38±0.08**,†††,†††
MG (mm Hg)	57±13.5†,†††,\$\$\$	64.4±16.3*,†††,\$\$\$	34.4±4.6***,†††	32.7±5.7***,†††
Vmax (m/s)	4.7±0.6†††,\$\$\$	4.9±0.6†††,\$\$\$	3.8±0.3***,†††	3.7±0.4***,†††
ELI (cm <sup>2</sup> /m <sup>2</sup> )	0.48±0.10†††,†††	0.27±0.06***,†††,\$\$\$	0.55±0.09***,†††,\$\$\$	0.43±0.10†††,†††
<b>LV global afterload</b>				
Z <sub>va</sub> (mm Hg/ml/m <sup>2</sup> )	4.1±0.8†††,\$\$\$	6.7±1.3***,†††	4±0.8†††,\$\$\$	5.5±1.1***,†††
SVR (mm Hg.min/l)	1315±355†††,†,\$\$\$	2028±528***,†††	1467±336*,†††,\$\$\$	1993±626***,†††
SAC (ml/mm Hg/m <sup>2</sup> )	0.83±0.32†††,†,\$\$\$	0.53±0.16***,††	0.71±0.24*,††,\$\$	0.54±0.20***,††
<b>LV Geometry</b>				
LVIDd (mm/m <sup>2</sup> )	27.5±4.5 ns	27.1±4	27.3±3.9	26.3±3.4
LVIDs (mm/m <sup>2</sup> )	16.7±3.8 ns	17.3±3.6	16.6±4.1	17.4±4
EDV <sub>i</sub> (ml/m <sup>2</sup> )	61.4±21.8†	52.8±21.5*	53.5±17.8	50.4±15.5
ESV <sub>i</sub> (ml/m <sup>2</sup> )	21±10.6 ns	19.5±10.7	19.8±10.2	19.7±8.1
LV mass index (g/m <sup>2</sup> )	143±46 ns	134±40	136±38	127±41
LVOT (mm)	21.6±2.2†††,\$\$\$	19.4±1.4***,†††	21.1±1.8†††	19.8±2***
Aortic diameter (mm)	34.1±5†	31.6±5*	33.5±5.9	31.6±4.4
<b>LV function</b>				
LVEF (%)	66.8±8 ns	63.7±8.2	64.6±7.3	63±9.3
SVi (ml/m <sup>2</sup> )	49.9±9.4†††,††,\$\$\$	30.4±3.4***,†††	45.2±7.1**,†††,\$\$\$	30.6±4.1***,†††
CO (l/min)	6.1±1.5†††,††,\$\$\$	3.8±0.8***,†††	5.4±1.1**,†††,\$\$\$	3.9±1***,†††
CI (l/min/m <sup>2</sup> )	3.4±0.8†††,†,\$\$\$	2.1±0.4***,†††	3±0.6*,†††,\$\$\$	2.1±0.5***,†††
SW (g.m)	181±52†††,†††,\$\$\$	118±28***,††,\$\$	144±34***,††,\$\$\$	95±22***,††,†††
SW/100g (g.m)	78±30†††,††,\$\$\$	53±19***	65±26**,\$\$	47±17***,††
MWFS (%)	22±6.4 ns	19.2±5.9	21.1±5.8	20.8±6.5

AVA indicates aortic valve area; AVAI, aortic valve area index; BSA, body surface area; CI, cardiac index; CO, cardiac output; DAP, diastolic arterial pressure; EDV<sub>i</sub>, end diastolic volume index; ELI, energy loss index; ESV<sub>i</sub>, end systolic volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter index in diastole; LVIDs, left ventricular internal diameter index in systole; LVOT, left ventricular outflow tract; MG, mean gradient; MWFS, midwall fractional shortening; SAC, systemic arterial compliance; SAP, systolic arterial pressure; SVi, stroke volume index; SVR, systemic vascular resistance; SW, stroke work; Vmax, maximal velocity; Z<sub>va</sub>, valvulo-arterial impedance.

1 symbol:  $P<0.05$ .

2 symbols:  $P<0.01$ .

3 symbols:  $P<0.001$ .

\*vs group 1.

†vs group 2.

‡vs group 3.

§vs group 4.

### Group 1 Patients: Normal Flow High Gradient

Two hundred and thirteen (62.7%, 95% CI: 57.3 to 67.8) patients matched the definition of group 1 (mean gradient >40 mm Hg and SVi >35 mL/m<sup>2</sup>). There was a high

proportion of men (69%), and a low proportion of diabetic patients (20%).

They were characterized by severe AS (AVA=0.79±0.17 cm<sup>2</sup>, aortic valve area index [AVAI]=0.44±0.08



**Table 4. Comparison of LV Strain Among the 4 Groups**

	Group 1 SVi>35 MG>40 n=213	Group 2 SVi≤35 MG>40 n=45	Group 3 SVi>35 MG≤40 n=52	Group 4 SVi≤35 MG≤40 n=30
GLS (%)	-16.5±3.4†††	-14.1±3.5***,††	-16.5±3.5††	-15.5±4.1
LS base (%)	-13.6±3.2†††,§	-10.9±2.8***,†††	-14.8±3.1†††,§§§	-11.6±3.4*,†††
LS mid-LV (%)	-15.8±3.1†††	-13.7±3.3***,†††	-16.8±3.2†††,§	-14.4±3.3‡
LS apex (%)	-22±5.5†	-19.5±4.9*	-21.2±6.1	-20.1±6.5
RS (%)	35.9±16.8	33±21	36.7±14.5§	27.9±10.5‡
CS (%)	-19.6±6 ns	-17.7±6.1	-18.3±5.6	-16.1±4.7

CS indicates circumferential strain; GLS, global longitudinal strain; LS, longitudinal strain; LV, left ventricular; MG, mean gradient; RS, radial strain; SVi, stroke volume index.

1 symbol:  $P<0.05$ .

2 symbols:  $P<0.01$ .

3 symbols:  $P<0.001$ .

\*vs group 1.

†vs group 2.

‡vs group 3.

§vs group 4.

$\text{cm}^2/\text{m}^2$ , mean gradient= $57\pm13.5$  mm Hg, energy loss index= $0.48\pm0.10$   $\text{cm}^2/\text{m}^2$ ), and normal LV afterload (valvulo-arterial impedance= $4.1\pm0.8$  mm Hg/mL/ $\text{m}^2$ ). LV end-diastolic diameter index and volume index (EDV<sub>i</sub>) were within the normal range. LV mass index was high ( $143\pm46$  g/ $\text{m}^2$ ).

LV systolic function was apparently normal with normal LVEF, cardiac index, and midwall fractional shortening (MWFS). However, longitudinal deformation was reduced, as attested by low GLS ( $-16.5\pm3.4\%$ ), particularly in the basal segments (basal longitudinal strain= $-13.6\pm3.2\%$ ).

### Group 2 Patients: Low Flow, High Gradient

Forty-five (13.2%, 95% CI: 9.8 to 17.3) patients matched the definition of group 2 (mean gradient  $>40$  mm Hg and SVi  $\leq 35$  mL/ $\text{m}^2$ ). The patients were more often women (56%), and they presented with the most severe form of AS.

AVA and AVAi were significantly lower than in group 1 (AVA= $0.46\pm0.11$   $\text{cm}^2$ ,  $P<0.001$ ; AVAi= $0.26\pm0.05$   $\text{cm}^2/\text{m}^2$ ,  $P<0.001$ ). They presented with the highest LV afterload, with a  $Z_{\text{va}}$  value significantly higher than in group 1 ( $6.7\pm1.3$  mm Hg/mL/ $\text{m}^2$ ,  $P<0.001$ ), and high systemic vascular resistance. LVEF did not differ from group 1, but end-diastolic volume index was significantly lower than in group 1 ( $52.8\pm21.5$  mL/ $\text{m}^2$ ,  $P<0.05$ ). SVi ( $30.4\pm3.4$  mL/ $\text{m}^2$ ,  $P<0.001$ ) and cardiac output ( $3.8\pm0.8$  l/min,  $P<0.001$ ) were significantly lower. Longitudinal function was more severely impaired than in group 1, concerning both GLS ( $-14.1\pm3.5\%$ ,  $P<0.001$ ) and basal longitudinal strain ( $-10.9\pm2.8\%$ ,  $P<0.001$ ).

### Group 3 Patients: Normal Flow, Low Gradient

Fifty-two (15.3%, 95% CI: 11.6 to 19.6) patients matched the definition of group 3 (mean gradient  $\leq 40$  mm Hg and SVi  $>35$  mL/ $\text{m}^2$ ).

There was a high proportion of hypertensive (78%) and diabetic (36%) patients in this group.

AS was less severe among these patients, with a higher AVA ( $0.86\pm0.14$   $\text{cm}^2$ ;  $P<0.01$  versus group 1,  $P<0.001$  versus group 2) and AVAi ( $0.49\pm0.07$   $\text{cm}^2/\text{m}^2$ ;  $P<0.001$  versus other groups), and a higher energy loss index

( $0.55\pm0.09$   $\text{cm}^2/\text{m}^2$ ,  $P<0.001$  versus other groups). Mean gradient ( $34.4\pm4.6$  mm Hg) was lower than in group 1 and 2 ( $P<0.001$  for both).

These patients presented with normal  $Z_{\text{va}}$  ( $4\pm0.8$  mm Hg/mL/ $\text{m}^2$ ), similar to group 1, and comparable LV geometry. LV systolic function was similar than in group 1, both in terms of LVEF, midwall fractional shortening, and degree of longitudinal dysfunction, as assessed by 2D strain. Global longitudinal strain ( $-16.5\pm3.5\%$ ) was similar to group 1, and significantly higher than in group 2 ( $P<0.01$ ). However, basal longitudinal strain ( $-14.8\pm3\%$ ) was higher than in group 1 and 2 ( $P<0.001$  for both). On the other hand, SVi ( $45.2\pm7.1$  mL/ $\text{m}^2$ ) was higher than in group 2 ( $P<0.001$ ), but lower than in group 1 ( $P<0.01$ ).

### Group 4 Patients: Low Flow, Low Gradient

Thirty (8.8%, 95% CI: 6.0 to 12.4) patients matched the definition of group 4: low flow low gradient (mean gradient  $\leq 40$  mm Hg and SVi  $\leq 35$  mL/ $\text{m}^2$ ). The proportion of hypertensive patients was the lowest (56%,  $P=0.04$ ), whereas there were more diabetic patients than in the other groups (41%,  $P=0.03$ ). The proportion of men was also high (63%).

Aortic stenosis severity based on AVAi was less severe than in group 2 ( $0.38\pm0.08$   $\text{cm}^2/\text{m}^2$ ,  $P<0.001$ ), but more severe than in group 1 and 3 ( $P<0.01$  and  $P<0.001$ , respectively). Mean gradient ( $32.7\pm5.7$  mm Hg) was lower than in group 1 and 2 ( $P<0.001$  for both).

These patients presented with elevated LV afterload ( $Z_{\text{va}}$   $5.5\pm1.1$  mm Hg/mL/ $\text{m}^2$ ) higher than in group 1 and 3 ( $P<0.001$ ), and showed no difference with group 2.

LVEF was  $63\pm9.3\%$ , and showed no difference with the other groups ( $p=\text{ns}$ ). SVi ( $30.6\pm4.1$  mL/ $\text{m}^2$ ) was significantly lower than in group 1 and 3 ( $P<0.001$ ), and showed no difference with group 2. Midwall fractional shortening was similar than in other groups. However, stroke work index was the lowest ( $47\pm17$  g.m,  $P<0.001$  versus group 1,  $P<0.01$  versus group 3).

Global longitudinal strain ( $-15.5\pm4.1\%$ ) and circumferential showed no difference with other groups. However, basal longitudinal strain was reduced in this group

( $-11.6 \pm 3.4\%$ ), significantly lower than in groups 1 ( $P < 0.05$ ) and 3 ( $P < 0.001$ ). After adjustment for age, sex, AVA, and  $Z_{va}$ , basal longitudinal strain in this group remained significantly lower than in groups 1 ( $P < 0.01$ ) and 3 ( $P < 0.01$ ). Radial strain also was significantly lower than in group 3 ( $27.9 \pm 10.5\%$  versus  $36.7 \pm 14.5\%$ ,  $P < 0.05$ ).

### Gender Differences Between Groups

Proportion of men was higher in the overall population (63%) and in the LFLG group (63%). In the overall population, despite similar aortic stenosis severity, LV hypertrophy and mass were significantly higher among men. Same results were observed in groups 1 and 3. In groups 2 and 4, however, no difference was observed between men and women regarding neither AS severity nor LV hypertrophy (Table 5).

### Reproducibility of Strain Measurements

Intra-observer, inter-observer, and interinstitutional reproducibility was good for GLS (ICC=0.95 [95% CI: 0.86 to 0.98], 0.94 [95% CI: 0.84 to 0.98], and 0.96 [95% CI: 0.86 to 0.99], respectively) and mean basal longitudinal strain (ICC=0.94 [95% CI: 0.84 to 0.98], 0.97 [95% CI: 0.94 to 0.99], and 0.97 [95% CI: 0.89 to 0.99], respectively), but lower for radial strain (ICC=0.76 [95% CI: 0.38 to 0.90], 0.70 [95% CI: 0.10 to 0.92], and 0.64 [95% CI: 0.04 to 0.91], respectively) and circumferential strain (ICC=0.77 [95% CI: 0.43 to 0.92], 0.76 [95% CI: 0.46 to 0.87], and 0.71 [95% CI: 0.32 to 0.90], respectively).

### Discussion

Our study presents one of the largest series of prospectively assessed patients with LF or low-gradient aortic stenosis. The main results of our study are as follows:

1. Patients with low-gradient severe AS and preserved LVEF can be subdivided into 2 groups depending on their stroke volume index.
  - a. Patients with low flow ( $\leq 35$  mL/m<sup>2</sup>) represent “true” severe low-flow low-gradient AS and represent only 8.8% of cases in our series. They are characterized by severe AS, elevated LV afterload, and impaired intrinsic LV myocardial function evidenced by speckle tracking imaging.
  - b. Patients with normal-flow AS are more frequent (15.3%) and present with less severe AS, normal LV afterload, and less severe LV dysfunction by 2D strain.
2. Subtle LV dysfunction can be evidenced by 2D strain in the majority of patients with severe AS and normal LVEF. Longitudinal LV dysfunction is particularly severe in AS with low cardiac output, including low-flow high-gradient and LFLG AS.

### Definition of Severe Aortic Stenosis

The definition of what a severe stenosis is has changed during the past years,<sup>1,16,17</sup> and it differs from one guideline to another.<sup>1,2</sup> Most recent guidelines consider an AS severe when valve area is  $<1$  cm<sup>2</sup>, indexed AVA  $<0.6$  cm<sup>2</sup>/m<sup>2</sup>, or mean gradient  $>40$  mm Hg. Although the American guidelines stipulate that “when stenosis is severe and cardiac output is normal, the mean transvalvular pressure gradient is generally greater than

**Table 5. Gender Differences Between the 4 Groups**

	Men	Women	P
<b>Group 1</b>			
N (%)	147 (69%)	65 (31%)	
Age (y)	70.2 $\pm$ 11.5	73.6 $\pm$ 12	0.047
AVA (cm <sup>2</sup> )	0.81 $\pm$ 0.18	0.73 $\pm$ 0.16	0.0009
AVAi (cm <sup>2</sup> /m <sup>2</sup> )	0.44 $\pm$ 0.08	0.44 $\pm$ 0.09	0.8
MG (mm Hg)	56.7 $\pm$ 13.7	57.5 $\pm$ 13.3	0.68
LV mass (g/m <sup>2</sup> )	151 $\pm$ 49	127 $\pm$ 34	0.0004
<b>Group 2</b>			
N (%)	20 (44%)	25 (56%)	
Age (y)	75 $\pm$ 9.1	75.3 $\pm$ 9.4	0.96
AVA (cm <sup>2</sup> )	0.57 $\pm$ 0.09	0.42 $\pm$ 0.10	0.0009
AVAi (cm <sup>2</sup> /m <sup>2</sup> )	0.27 $\pm$ 0.05	0.25 $\pm$ 0.06	0.14
MG (mm Hg)	60.2 $\pm$ 15.5	67.8 $\pm$ 16.4	0.13
LV mass (g/m <sup>2</sup> )	132 $\pm$ 40	136 $\pm$ 41	0.75
<b>Group 3</b>			
N (%)	29 (54%)	24 (46%)	
Age (y)	73.7 $\pm$ 9.6	74.5 $\pm$ 10.9	0.75
AVA (cm <sup>2</sup> )	0.89 $\pm$ 0.15	0.83 $\pm$ 0.10	0.11
AVAi (cm <sup>2</sup> /m <sup>2</sup> )	0.48 $\pm$ 0.07	0.50 $\pm$ 0.07	0.2
MG (mm Hg)	34.5 $\pm$ 4.4	34.1 $\pm$ 4.9	0.74
LV mass (g/m <sup>2</sup> )	152 $\pm$ 39	117 $\pm$ 24	0.0004
<b>Group 4</b>			
N (%)	19 (63%)	11 (37%)	
Age (y)	73 $\pm$ 17.7	77.5 $\pm$ 7	0.43
AVA (cm <sup>2</sup> )	0.71 $\pm$ 0.13	0.68 $\pm$ 0.11	0.57
AVAi (cm <sup>2</sup> /m <sup>2</sup> )	0.37 $\pm$ 0.08	0.40 $\pm$ 0.07	0.38
MG (mm Hg)	34.3 $\pm$ 5.2	29.9 $\pm$ 5.4	0.04
LV mass (g/m <sup>2</sup> )	131 $\pm$ 41	121 $\pm$ 44	0.50
<b>Overall</b>			
N (%)	215 (63%)	125 (37%)	
Age (y)	71.4 $\pm$ 11.8	74.5 $\pm$ 10.9	0.016
AVA (cm <sup>2</sup> )	0.79 $\pm$ 0.19	0.68 $\pm$ 0.19	$<0.0001$
AVAi (cm <sup>2</sup> /m <sup>2</sup> )	0.42 $\pm$ 0.10	0.41 $\pm$ 0.12	0.34
MG (mm Hg)	52.1 $\pm$ 15.6	52.6 $\pm$ 17.9	0.76
LV mass (g/m <sup>2</sup> )	147 $\pm$ 46	126 $\pm$ 35	$<0.0001$

AVA indicates aortic valve area; AVAi, aortic valve area index; LV, left ventricular; MG, mean gradient.

40 mm Hg”, the clinical practice is quite different. This definition has been questioned in the past few years for the following reasons.<sup>3,4</sup>

Discrepancies between gradient and surface are frequent, even in patients with an apparently normal LV function. It was observed in 35% of patients in the series of Hachicha et al,<sup>7</sup> 30% in the series of Minners et al,<sup>3</sup> and 24% in our series. The most frequent condition is represented by patients with low gradient despite severe AS and apparently normal LV function. In a series of 512 consecutive patients with severe AS and LVEF  $>50\%$ , Hachicha observed that these patients were characterized by lower LV volumes, higher LV afterload, and low 3-year survival.

However, other authors reached different conclusions. Minners et al,<sup>3</sup> in a series of 2427 severe AS with normal LV

function, found 30% of such inconsistent findings, and remind that, according to previous studies using Gorlin formula,<sup>18</sup> an AVA of 1 cm<sup>2</sup> corresponds to a gradient of only 26 mm Hg. Thus, if these discrepant gradings may be explained by reduced stroke volume, they rather proposed a cut-off value of 0.8 cm<sup>2</sup> to define severe AS.

Similarly, Janders<sup>4</sup> underlined that, if these inconsistent grading could be related to “paradoxical” low flow, inaccurate measurements of AVA and inconsistent cut-off values may also contribute to inconsistent severity grading. He proposed that a transesophageal echocardiographic examination should be added to assess morphology of the aortic valve and obtain a more precise measurement of the left ventricular outflow tract diameter.<sup>4</sup>

Finally, several patients with severe AS and preserved LV function do not fit in the “low flow low gradient” category. A significant number present with low flow ( $\leq 35$  mL/m<sup>2</sup>) but high gradient, while another group present low gradient despite normal flow.<sup>4</sup> This latter group possibly represents nonsevere AS, and it is crucial to clearly identify these patients, because therapeutic strategy could be different.

More recently, Dumesnil et al<sup>5</sup> reassessed their series of 512 patients and separated them into 4 subgroups according to presence of normal or reduced flow (SVI  $>$  or  $\leq 35$  mL/m<sup>2</sup>) and high or low gradient ( $>$  or  $\leq 40$  mm Hg). They clearly confirmed that low gradient could be observed in some patients with normal flow and that, conversely, high gradient could be observed in some patients with low flow.

### Low-Gradient AS

Our results confirm the series of Dumesnil et al, showing that low-gradient AS despite normal LVEF was a frequent finding, representing 24% of all cases of aortic stenosis with normal LVEF. This pattern has been observed in up to 35% of patients with severe AS and normal LVEF and has been shown to be associated with higher global LV afterload, more pronounced concentric remodelling, and lower survival if not operated.<sup>7</sup>

However, the main result of our study is that the incidence of “true severe” LFLG AS was lower, representing only 8.8% of the patients. It is interesting to note that this low percentage was similarly observed in each of the 5 centers involved in the study (Table 2). As observed by Hachicha et al,<sup>7</sup> these patients are characterized by their advanced age, severe AS (AVA =  $0.38 \pm 0.08$  cm<sup>2</sup>/m<sup>2</sup>), nondilated left ventricles, and low cardiac output. As in previous reports, we found that the main mechanism for the low cardiac output was elevated global afterload as attested by high  $Z_{va}$ , high vascular resistance, and reduced arterial compliance. In addition, left ventricular dysfunction despite normal LVEF was evidenced by 2D strain imaging, showing reduced longitudinal contraction, particularly among the basal segments. The lower incidence of LFLG in our series as compared with the series of Hachicha probably reflects differences in patient recruitment. However, in the most recent series from the same center,<sup>5</sup> LFLG AS represented only 24% of all AS with normal LVEF.

Conversely, we observed that a larger number of patients (15.3%) presented with low gradient, but did not fulfill the criteria for LFLG AS, because they presented with normal flow. As compared with LFLG AS, these patients were quite different,

with less severe AS, normal LV afterload, and less depressed longitudinal function, as assessed by 2D strain (Figure). Although these patients have severe AS in terms of AVA, this stenosis is less severe than in other groups. It has been proposed that the discrepancy between low gradient and low AVA could be related to inaccurate echocardiographic measurement of the left ventricular outflow tract or inconsistent cut-off values of gradient and AVA in current recommendations.<sup>4</sup> These patients represent up to 38% of AS with normal LVEF in the recent series of Dumesnil et al,<sup>5</sup> who confirmed the lower degree of severity of AS in this group in their series.

### Role of Speckle-Tracking Imaging in Assessing Left Ventricular Function in LFLG AS

The presence of LV dysfunction despite normal LVEF in aortic stenosis has been proved by several studies. It was first suspected by the presence of a low midwall fractional shortening,<sup>7,9</sup> and more recently by the evidence of LV longitudinal dysfunction despite normal LVEF in AS by 2D strain studies.<sup>10,11</sup> LV longitudinal contraction is impaired early in situations of high afterload<sup>19</sup> and thus could be potentially particularly impaired in the subgroup of patients with LFLG AS, which are characterized by elevated afterload. Speckle-tracking imaging recently has been applied to patients with LFLG AS. In a series of 173 patients with severe asymptomatic AS, Lancellotti et al<sup>12</sup> found that intrinsic myocardial dysfunction, as assessed by 2D strain, was particularly common in patients with increased global LV afterload, especially in the subset of patients with low-flow AS. However, in these studies, the number of patients with low-flow and low-gradient AS was low.

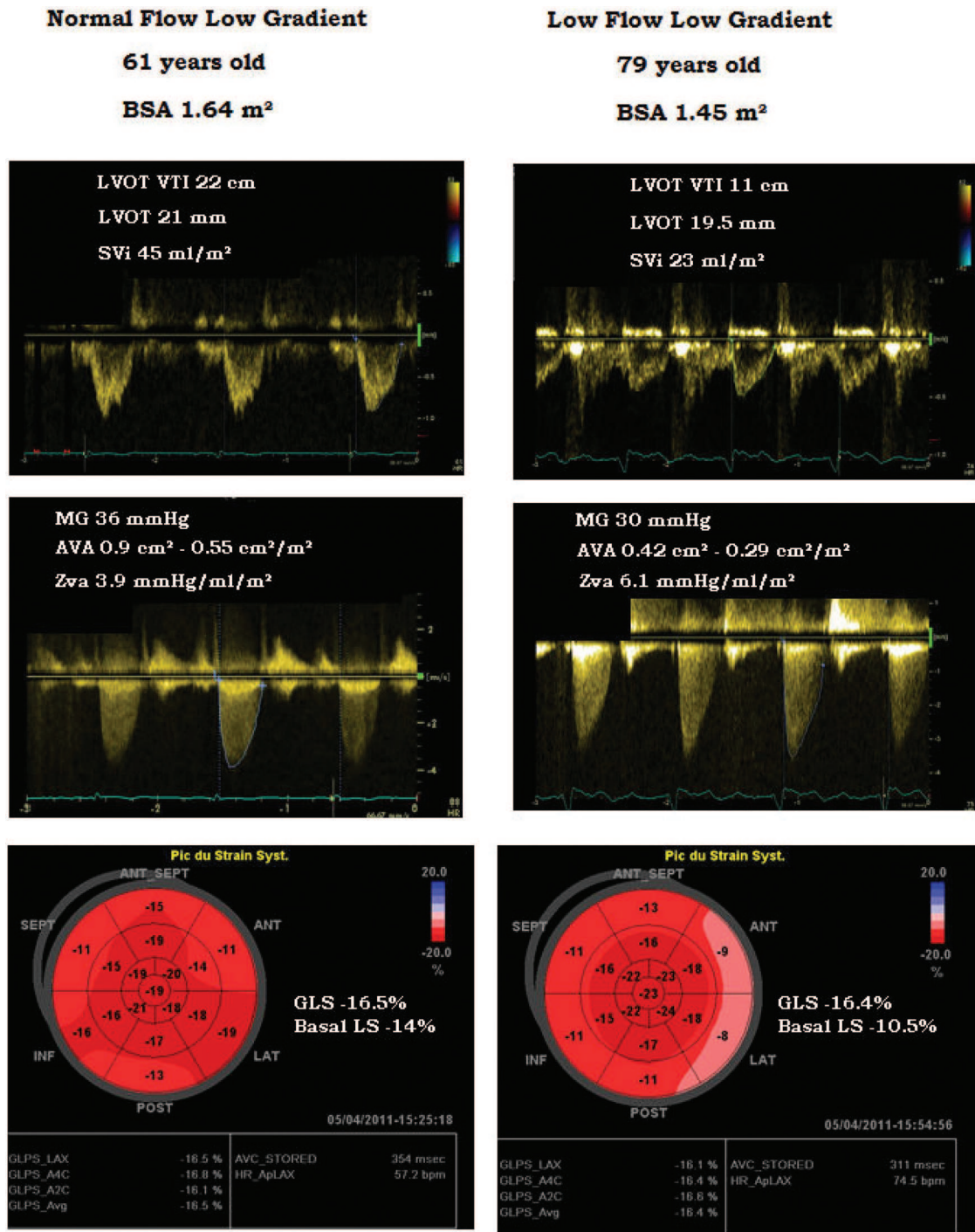
Our study is the first large multicenter study to prospectively assess the value of 2D strain in assessing early LV dysfunction in these patients. We found that longitudinal dysfunction was very common in all 4 groups of patients with AS and normal LVEF, but that LV longitudinal function was particularly impaired in the 2 groups with high afterload, that is patients with low-flow high-gradient and LFLG AS (groups 2 and 4). Interestingly, LV longitudinal dysfunction was clearly more marked in group 4 (LFLG AS) than in group 3 (NFLG AS), confirming that the hemodynamic status and severity of AS of both groups are quite different. The fact that this difference was particularly evidenced on longitudinal strain, and less in its radial component, probably reflects the earlier impairment of longitudinal function in these patients. In addition, the better intra-observer, inter-observer, and interinstitutional reproducibility observed in our study for longitudinal strain as compared with radial and circumferential strain is in favor of the preferential use of longitudinal strain for early detection of left ventricular dysfunction in patients with AS.

### Clinical Implications

In clinical practice, when facing patients with severe AS and low gradient despite normal left ventricular ejection fraction, 2 parameters are of major importance for differentiating patients with LFLG AS from patients with NFLG AS.

1. Valvulo-arterial impedance allows an evaluation of LV afterload. It is significantly elevated in LFLG AS, and has been shown to be an independent prognostic factor.<sup>7</sup>





**Figure.** Illustrative cases of 2 patients with normal flow low gradient (left panel) and low flow low gradient (right panel) aortic stenoses with normal ejection fraction. Although both patients present with severe aortic stenosis (aortic valve area  $<1$  cm<sup>2</sup> and indexed aortic valve area  $<0.6$  cm<sup>2</sup>/m<sup>2</sup>), the patient with low flow low gradient (right panel) is characterized by a lower stroke volume index (upper panels), higher valvulo-arterial impedance (middle panels), and lower basal longitudinal strain (lower panels) as compared with the patient with normal flow low gradient (left panel) aortic stenosis.

- 2D strain allows an evaluation of LV longitudinal dysfunction. Longitudinal dysfunction is more severe in patients with LFLG AS than in patients with NFLG AS.

The combined evaluation of global afterload (by valvulo-arterial impedance measurement) and of longitudinal systolic function (by 2D strain measurements) provides an optimal assessment of patients with low-gradient severe AS despite

normal LV ejection fraction. This evaluation may help in separating patients with low-gradient AS into 2 groups of different severity.

## Conclusions

LFLG AS is observed in 9% of patients with severe AS and normal ejection fraction and is characterized by elevated

global afterload and reduced longitudinal systolic function. Patients with normal-flow low-gradient AS are more frequent and present with less severe AS, normal LV afterload, and less severe LV dysfunction by 2D strain. In addition to elevated afterload, the severe longitudinal dysfunction documented by 2D strain gives a new explanation to the concept of LFLG AS. The prognostic significance of these findings needs further investigation.

## Disclosures

None.

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## CLINICAL PERSPECTIVE

In a multicenter study concerning low-flow low-gradient aortic stenosis (LFLG AS) despite normal ejection fraction, the role of speckle tracking echocardiography in detecting subtle left ventricular dysfunction is reported. In addition to elevated afterload, the severe longitudinal dysfunction documented by 2D strain in these patients gives a new explanation to the concept of LFLG AS. The main findings of our study are twofold. First, among patients with severe AS, low gradient, and normal LV ejection fraction, 2 different patterns can be observed, with different hemodynamic characteristics and aortic severity. LFLG AS is observed in 9% of patients and is associated with high global afterload and reduced longitudinal systolic function. Patients with NFLG AS are more frequent and present with less severe AS, normal afterload, and less severe longitudinal dysfunction. Second, in clinical practice, 2 parameters are of major importance in the evaluation of patients with low-gradient severe aortic stenosis despite normal ejection fraction. Valvulo-arterial impedance allows an evaluation of LV afterload. It is significantly elevated in LFLG AS, and has been shown to be an independent prognostic factor. LV longitudinal dysfunction can be observed by 2D strain and is more severe in patients with LFLG AS as compared with other groups. The combined evaluation of global afterload (by valvulo-arterial impedance measurement) and of longitudinal systolic function (by 2D strain measurements) provides an optimal assessment of patients with low-gradient severe AS despite normal LV ejection fraction. This evaluation may help in separating patients with low-gradient AS into 2 groups of different severity.